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USSN: 09/546,201
Dkt. No.: PP01463.002
2300-1463

PATENT

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7/27/05 Michelle Hobson

Date Signature

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of:	Examiner: S. Foley
POLO et al.	Group Art Unit: 1648
Serial No.: 09/546,201	Confirmation No.: 3605
Filing Date: April 10, 2000	Customer No.: 20855
Title: ENHANCEMENT OF THE IMMUNE RESPONSE FOR VACCINE AND GENE THERAPY APPLICATIONS	

TRANSMITTAL LETTER

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313

Sir:

Transmitted herewith for filing, please find the following documents:

X Appeal Brief (17 pgs) with attached Claims Appendix (4 pgs), Evidence Appendix (1 pg) and Related Proceedings Appendix (1 pg)

X Return receipt postcard

The fee is calculated as follows:

	NO. OF CLAIMS	CLAIMS PREVIOUSLY PAID FOR	EXTRA CLAIMS	RATE	FEE
Total Claims	17	- 20	0	x $50.00	$0
Independent Claims	1	- 3	0	x $200.00	$0
Multiple dependent claims not previously presented, add $360.00					$0
Total Amendment Fee					$0
Petition for Extension of Time Fee					$0
Appeal Brief Fee					$500.00
Small Entity Reduction (if applicable)					$0
TOTAL FEE DUE					$500.00

X A check in the amount of $500.00.

The Commissioner is hereby authorized to charge any appropriate fees under 37 C.F.R. §§1.16, 1.17, and 1.21 that may be required by this paper, and to credit any overpayment, to Deposit Account No. 18-1648.

Respectfully submitted,

Date: July 27, 2005

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APPEAL BRIEF

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APPEAL BRIEF

Mail Stop Appeal Brief
Commissioner for Patents
Alexandria, VA 22313

Sir:

INTRODUCTION

Appellants submit one copy of their brief on appeal in accordance with Section 41.37 (69 Fed. Reg. 49962, Aug 2004). All claims were finally rejected under 35 U.S.C. § 103 in a Final Office Action dated January 25, 2005. A Notice of Appeal was filed May 31, 2005, making an Appeal Brief due on or before July 31, 2005. Accordingly, this Brief is timely filed. Appellants respectfully request that the decision of the Examiner be reversed.

I. REAL PARTY IN INTEREST

Chiron Corporation, the assignee of record of the above-referenced patent application, is the real party in interest in this matter.

II. RELATED APPEALS AND INTERFERENCES

Appellants are not aware of any related appeals or interferences.

III. STATUS OF THE CLAIMS

Claims 26, 28-31 and 33-44 are currently pending in the above-referenced case (hereinafter "the application"). The application was originally filed on April 10, 2000 with claims 1-45. In response a Restriction Requirement (mailed on December 6, 2000), claims 26 and 28-44 were elected, without traverse. Claims 1-25, 27, 32 and 45 were canceled, without prejudice or disclaimer, in an Amendment submitted on August 10, 2001. Claim 43 was amended in an Amendment submitted on April 4, 2002 and claim 26 was amended in papers submitted on October 1, 2002, November 26, 2003 and April 26, 2004. Accordingly, claims 26, 28-31 and 33-44 are pending as shown in the Claims Appendix. Claims 26, 28-31 and 33-44 remain rejected under 35 U.S.C. § 103(a).

IV. STATUS OF THE AMENDMENTS

In response to the Examiner's Final Office Action mailed January 25, 2005, Appellants filed a Response with arguments and no amendments. An Advisory Action was mailed on June 20, 2005. Thus, all claims remained rejected for the reasons set forth in the Final Office Action and Advisory Action and have not been amended since the Final Office Action.

V. SUMMARY OF THE CLAIMED SUBJECT MATTER

The claimed subject matter relates to an expression cassette comprising (i) a promoter operably linked to a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences within the RNA, wherein the double stranded RNA induces the production of interferon (page 3, lines 16-20 and 26-57; page 4, lines 19-20), and (ii) an RNA polymerase II promoter (*e.g.*, CMV, SV40, MoMLV LTR and RSV LTR) operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent (page 4, lines 20-22; page 5, line 5).

In certain embodiments, the antigen is a viral antigen (page 13, lines 1-12), for example, HIV, HSV, HBV, HCV, HPV, and FIV (page 13, lines 1-8). In other embodiments, the pathogenic agent is a bacteria, parasite or fungus (page 12, line 29) or a tumor (page 12, line 17; page 20, lines 18-22).

The claimed subject matter also relates to a gene delivery vector, comprising an expression cassette as described above (page 5, lines 17-18; page 7, line 28 to page 8, line 12). The gene delivery vector may be a plasmid, a recombinant retrovirus, a recombinant herpesvirus, a recombinant poxvirus, a recombinant adenovirus, a recombinant parvovirus, a recombinant alphavirus, a recombinant polyoma virus, or a eukaryotic layered vector initiation system vector (page 5, lines 19-21; page 17, line 22 to page 19, line 4).

The invention also relates to a cell containing a gene delivery vector as described above (page 5, lines 22-25).

VI. GROUNDS OF REJECTION

1. Claims 26, 28-31 and 33-44 stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"), Cella et al. (1999) *J. Exper. Med.* 189(5):821-829 (hereinafter "Cella"), U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie").

VII. ARGUMENTS

1. A *Prima facie* Case of Obviousness Has Not been Established

All of the pending claims remain rejected as allegedly obvious over U.S. Patent No. 6,015,686 (hereinafter "Dubensky"); Cella et al. (hereinafter "Cella") and U.S. Patent No. 5,736,388 (hereinafter "Chada") and WO 90/14090 (hereinafter "Gillespie").

In support of the rejections, the Examiner has repeatedly asserted that Dubensky and Chada teach expression vectors comprising multiple genes and that it would have been obvious to replace antisense RNA as disclosed in Dubensky and Chada with dsRNA formed by self-complementation as disclosed in Gillespie (see, e.g., Advisory Action mailed June 20, 2005, emphasis added):

> Dubensky and Chada teach expression of multiple heterologous genes from the same construct. Dubensky explicitly teaches that the expression vector is used to express multiple heterologous genes [citations omitted]. Chada also teaches a eukaryotic layered vector initiation system that utilizes the same viral vectors and the same promoters of Dubensky [citation omitted]. Chada states that one promoter within the same construct may be inadequate to ensure an adequate level of expression of all heterologous genes [citation omitted]. This express teaching provides explicit motivation to express multiple heterologous genes of Dubensky from different promoters within the same construct. ...
>
> Therefore, the dsRNA of Dubensky and the self-complementing dsRNA of Gillespie are prima facie obvious alternatives.

Appellants submit the Examiner has improperly construed the claims and has used prohibited hindsight reconstruction in making these rejections, as there is no combination of these references that results in the claimed subject matter and no teaching, suggestion or motivation within the cited references (or the art) to support the rejection.

The Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Ryckaert,* 28 USPQ2d 1955, 1956 (Fed. Cir. 1993); and *In re Oetiker,* 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). In addition, the law is well settled that references must teach all the limitations of the claimed invention and, moreover, suggest the desirability of arriving at the claimed subject matter. (*See, e.g., Amgen, Inc. v. Chugai Pharm. Co.,* 18 USPQ2d 1016, 1023

(Fed. Cir. 1991) stating that "hindsight is not a justifiable basis on which to find that the ultimate achievement of a long sought and difficult scientific goal was obvious;" *In re Laskowski,* 10 USPQ2d 1397, 1399 (Fed. Cir. 1989) stating that "the mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification"; and *In re Fulton*, 391 F.3d 1195 (Fed. Cir. 2004) stating that "[t]he question is whether there is something in the prior art as a whole to suggest the desirability").

In the pending case, the Examiner has not met this burden and the rejection cannot be maintained.

(a) The Claims Are Drawn to Particular Expression Cassettes Not Taught or Suggested by the References

In order to determine the relevance of any reference or combination of references, it is always first necessary to properly construe the claims. In the pending case, the Examiner has repeatedly asserted that the claimed expression cassettes express multiple genes. In other words, the claim recitation of a sequence that, "when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences" has been interpreted by the Examiner to be a "gene."

In reality, this element of the claimed expression cassettes is not a gene, as it does not encode (directly or via RNA intermediates) for a protein. Thus, in addition to comprising sequences that do encode for genes (*e.g.,* antigens), the claimed expression cassettes also require the expression of a particular non-gene, *i.e.,* a sequence that forms double stranded RNA via self-complementation. As such, the claims have been improperly construed to be drawn to expression cassettes that express multiple genes. When properly construed, the claims relate to an expression cassette comprising a gene (antigen-encoding) sequence and a non-gene sequence.

Indeed, Dubensky and Chada, the primary references cited against Appellants, support Appellants' position that those skilled in the art did not view antisense or other non-coding sequences as "genes." In particular, Dubensky clearly separates genes and antisense RNA,

discussing multiple genes in Section D.6 (Other Alphavirus Constructs; Multiple Heterologous Genes) and antisense RNA in Section E.4 (Heterologous Sequences; Antisense). *See,* cols. 16-18 and 22-23 of Dubensky. Antisense sequences are not genes and, accordingly, are discussed and defined separately.

Likewise, Chada defines a gene transfer systems as follows (col. 5, lines 7-10 of Chada, emphasis added):

> A "gene transfer system" refers to a construct which is capable of delivering, and, within preferred embodiments expressing, one or more gene(s) **or** sequence(s) of interest in a host cell.

Again, as with Dubensky, Chada confirms that the field as a whole considered sequences encoding genes and sequences expressing antisense RNA to be alternatives, not synonyms.

Simply put, as evidenced by the very references cited against Appellants, the skilled artisan would know the claims as pending are not directed to expression cassettes comprising sequences encoding multiple heterologous genes. Accordingly, any disclosure of expression vectors expressing multiple genes (as in Dubensky and Chada) is not relevant to the claims on appeal.

In addition to misconstruing the term "gene," the Examiner has also improperly construed the claims to encompass any double stranded RNA (dsRNA) molecules, no matter how the dsRNA is formed (antisense hybridization of heterologous antisense with endogenous mRNA or self-complementation) or how it is made (*in vivo* or *in vitro*). In fact, the claims require that the non-gene sequence of the expression cassette form dsRNA via self-complementation when transcribed *in vivo*. Thus, the Examiner's reading of the term "a sequence which forms double-stranded RNA via self-complementation" to somehow encompass double stranded RNA formed by binding of specific antisense RNA to endogenous mRNA or dsRNA formed via self-complementation *in vitro* is untenable. The claims are clear on their face that the type of dsRNA encompassed is only self-complementing dsRNA formed *in vivo*. Indeed, the claims necessarily

exclude both dsRNA formed by the binding of heterologous antisense RNA to endogenous mRNA and dsRNA formed by self-complementation *in vitro*.

Once again, the references cited by the Office support the conclusion that the Examiner's construction of the phrase "a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences within the RNA" to include antisense or dsRNA formed *in vitro* is in error. In particular, Dubensky is clear that the double stranded RNA is formed, not by self-complementation as claimed, but by the **specific** binding of **specific** antisense molecules to endogenous mRNA (Dubensky, col. 23, lines 1-12, emphasis added):

> In addition, within a further embodiment of the invention, antisense RNA may be utilized as an anti-tumor agent in order to induce a potent Class I restricted response. Briefly, in addition to binding RNA and thereby preventing translation of a specific mRNA, high levels of **specific antisense sequences** are believed to induce the increased expression of interferons (including gamma-interferon) **due to the formation of large quantities of double-stranded RNA**. The increased expression of gamma interferon, in turn, boosts the expression of MHC Class I antigens. **Preferred antisense sequences for use in this regard include actin RNA, myosin RNA, and histone RNA. Antisense RNA which forms a mismatch with actin RNA is particularly preferred**.

For its part, Gillespie makes it plain that dsRNA formed by self-complementation should be produced *in vitro* prior to administration to a live subject (Gillespie, page 7, lines 16-22; page 8, lines 7-14, claims 9-16; claims 9-16):

> The antitumor properties of dsRNA can be evaluated by exposing tumor cells is tissue culture to dsRNA and measuring reading in growth rate [citation omitted]. The antitumor properties of dsRNA can also be measured by injecting dsRNA into nude mice bearing tumors and measuring tumor growth rate.
>
> Suitable test animals such as mice, rats, rabbits, dogs, monkeys, etc. or humans can be injected periodically with various quantities of dsRNA ...
>
> ...which method comprises administering to the human a therapeutically effective amount of the short dsRNA of defined structure according to claim ...

In sum, the claims are not directed to generally to expression cassettes encoding multiple heterologous genes. Rather, they are directed to particular, expression cassettes encoding a particular antigen and a sequence that forms double-stranded RNA *in vivo* via self-complementation. It is impermissible for the Examiner to ignore any of the limitations that define the claimed expression cassettes. Accordingly, isolated disclosures of expression cassettes comprising sequences encoding multiple genes, expression cassettes comprising antisense sequences or even sequences that form double-stranded RNA via self-complementation *in vitro* cannot teach, suggest or provide the motivation to arrive at the particular expression cassettes claimed by Appellants.

(b) The Rejection Is Based On An Improper Combination of Individual Elements

When the claims are properly construed, it is clear that the combination of references does not teach an expression cassette as claimed, which expresses both an antigen (gene) and a sequence which forms, *in vivo*, dsRNA via self-complementation.

It is axiomatic that statements in the prior art must be considered in the context of the teaching of the entire reference, and that rejection of claims **cannot** be predicated on mere identification in a reference of individual components of claimed limitations. In this regard, the Federal Circuit has consistently reversed a finding of obviousness, even when all claimed elements are individually present in the references. *See, e.g., In re Kotzab* 217 F.3d 1365, 55 USPQ2d 1313, 1317 (CAFC 2000, emphasis added):

> While the test for establishing an implicit teaching, motivation or suggestion is what the combination of these two statements [in the reference] would have suggested to those of ordinary skill in the art, the two statements cannot be viewed in the abstract. Rather, they must be considered in the context of the teaching of the entire reference. Further, a rejection **cannot** be predicated on the mere identification [in the reference] of individual components of claimed limitations. Rather, particular findings must be made as to the reason the skilled artisan, with no knowledge of the claimed invention, would have selected these components for combination in the manner claimed.

Virtually all inventions are combinations of old elements. See, e.g., *In re Rouffet*, 47 USPQ2d 1453 (Fed. Cir. 1998) noting that the Office cannot rely on a high level of skill in the art to overcome the differences between the selected elements in the references, it cannot rely on a high level of skill in the art to provide the necessary motivation; *In re Lee*, 61 USPQ2d 1430 (Fed. Cir. 2002), affirming that common knowledge and common sense are not the specialized knowledge and expertise necessary to establish a motivation to arrive at the claimed invention.

Thus, the requirement is not whether each claimed element can be identified individually in a reference but, rather, whether the Examiner can show "reasons that the skilled artisan, confronted with the same problem as the inventor, and with no knowledge of the claimed invention, would select the elements from the cited prior art reference for combination in the manner claimed." *In re Rouffet*, 47 USPQ2d at 1458.[1]

In the pending case, the Office has not met this burden. As acknowledged, Dubensky and Chada do not teach or suggest expression vectors comprising (i) a promoter operably linked to a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded self-complementing RNA and (ii) an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent. Furthermore, it is acknowledged that the secondary references (Gillespie and Cella) fail to teach a vector expressing multiple sequences of any sort.

Nonetheless, the Examiner has continually relied on Dubensky for allegedly disclosing alphavirus vectors that express multiple heterologous genes. *See, e.g.*, text of Advisory Action, reproduced above with added emphasis. In this regard, the Examiner cited claim 10 in the Advisory Action as allegedly establishing that Dubensky contemplated expression vectors in which "heterologous sequences" included, in the same vector, coding and non-coding sequences.

In fact, as noted above with regard to claim construction, Dubensky clearly separates

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[1] Furthermore, it is clear that The Examiner's reliance on *In re McLaughlin*, 170 USPQ 209 (CCPA 1971) is entirely misplaced. See, Advisory Action, page 5. *McLaughlin* in no way held that common knowledge is a substitute for evidence, for example as required by 37 C.F.R. 1.104(d)(2). Nor does *McLaughlin*, after 32 years, outweigh the many Federal Circuit and CCPA decisions that the prior art as a whole must suggest the desirability of the making the claimed combination.

genes and antisense RNA and provides no reasons to combine them into a single vector. Furthermore, contrary to the Examiner's assertion on page 3 of the Advisory Action, Dubensky's claim 10 provides no teaching or suggestion to replace dsRNA for one of the multiple heterologous genes. Just as Dubensky separates multiple heterologous genes from heterologous sequences in the body of the specification, claim 10 relates to a eukaryotic layered vector initiation system (ELVIS) vector comprising, at best, multiple non-genes (antisense, noncoding sense or ribozyme). Like Dubensky as a whole, claim 10 teaches nothing about an expression vector comprising both gene and non-gene sequences, as claimed.

Thus, it is error to assert that Dubensky or Chada teach anything about putting both antigen-encoding and antisense sequences in the same vector. As admitted by the Office, this critical feature is also not taught or suggested by any of the other cited references. Therefore, this rejection can only be predicated on the mere identification of individual components without the motivation to combine them into the expression cassettes as claimed. This is entirely improper and, on this basis alone, the rejection should be withdrawn.

(c) There Is No Motivation To Combine the References As Set Forth In The Rejection

Even assuming, for the sake of argument only, that Dubensky did suggest an expression cassette that expressed both a heterologous antigen and antisense RNA (which it does not), the rejection is still unsustainable because there is no reasonable basis for substituting a sequence that, when transcribed *in vivo*, forms dsRNA via self-complementation for Dubensky or Chada's specific antisense sequences.

As acknowledged, Dubensky and Chada are silent as to dsRNA that when transcribed *in vivo* forms dsRNA via self-complementation. Furthermore, Cella discloses poly I:C dsRNA, but does not indicate whether the molecules are formed from self-complementation or, more likely,

by hybridization.[2] Thus, Dubensky, Chada and Cella fail to teach one of skill in the art anything regarding dsRNA formed by self-complementation and cannot provide the motivation to replace antisense sequences with dsRNA formed *in vivo* via self-complementation.

For its part, Gillespie is silent about antisense RNA and, in addition, fails to teach or suggest anything about dsRNA that forms *in vivo* via self-complementation. Indeed, Gillespie's entire section regarding "Types of dsRNA" (page 3, line 23 to page 5, line 1) contains not a word about antisense RNA, let alone any teachings that antisense RNA is somehow equivalent to the self-complementing dsRNA. Gillespie also fails to teach that dsRNA formed via self-complementation can be formed *in vivo*.

Thus, none of the references teach or suggest that antisense RNA and dsRNA formed *in vivo* via self-complementation are somehow interchangeable. Accordingly, the Examiner's assertions that (1) Gillespie's production of dsRNA in a host cell system is "*in vivo*" transcription from a vector and (2) Cella need not teach production of self-complementing dsRNA from a vector because Gillespie and Dubensky do are both incorrect. (Advisory Action, pages 4-5).

With respect to point (1), Gillespie is silent as to *in vivo* transcription, teaching only that dsRNA formed *in vitro* using a host cell system is subsequently administered to a human "in need for such therapy." *See, also,* page 7 above. With regard to point (2), because Dubensky relates only to production of antisense RNA from a vector and because Gillespie teaches that their *in vitro* systems represent a marked departure from art-accepted enzymatic methods used to make the dsRNA of Cella, Appellants submit that, in order to have any relevance to the claims on appeal, Cella is required to teach about self-complementing dsRNA and about production from vectors.

In any event, the fact remains that none of the cited references teach or suggest *in vivo* production of self-complementing dsRNA. Absent any teaching or suggesting to prepare expression cassettes comprising gene and non-gene sequences; and nucleic acid molecules that

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[2] In fact, Gillespie plainly teaches that polyI:C molecules such as those used in Cella are long dsRNA molecules made by enzymatic synthesis. *See, e.g.,* pages 1-2 of Gillespie. Therefore, a skilled artisan would conclude that Cella does not teach or suggest dsRNA formed by self-complementation, as claimed.

form dsRNA via self-complementation when transcribed *in vivo*, the rejection can only be based on improper hindsight reconstruction and, accordingly, should be withdrawn.

(d) The Motivation to Combine Cannot Derive From Inducing Production Of Interferon

Despite the complete failure of the references to teach or suggest expression cassettes that express gene and non-gene or to even hint at any relationship between antisense RNA and dsRNA formed *in vivo* via self-complementation, the Examiner has continually asserted that the motivation to substitute self-complementing sequences for antisense sequences of Dubensky and Chada lies in the fact that antisense RNA and self-complementing dsRNA are both capable of inducing interferon production. *See,* Advisory Action, page 4 stating that "dsRNA of Dubensky and the self-complementing dsRNA of Gillespie are prima facie obvious alternatives."

However, the evidence of record clearly indicates that the ability to induce interferon production is **not** a sufficient grounds to assert that an antisense-mRNA molecule is necessarily an "obvious alternative" to dsRNA formed *in vivo* by self-complementation. Not only is there nothing in Dubensky, Chada or Cella regarding dsRNA formed via self-complementation, Dubensky explicitly teaches that increased expression of interferons results from "large quantities" of double-stranded antisense-mRNA molecules and, indeed, indicates that in order to have sufficiently large quantities of the antisense-mRNA hybrids, antisense RNA that is specific for common mRNA transcripts (actin, myosin, histone) is preferred. *See, also,* page 7 above. Thus, Dubensky plainly teaches that large quantities of long antisense molecules are required to produce dsRNA in sufficient quantities to induce interferon production. Indeed, Dubensky teaches that interferon production is predicated on the antisense RNA of the expression cassette being a highly represented mRNA species, such as actin. *See,* Dubensky col. 23, reproduced in part above.

Gillespie, the only reference that teaches dsRNA formed via self-complementation, does not actually demonstrate that such sequences actually induce interferon production. Rather,

Gillespie teaches that their invention is a "means for synthesizing stable short dsRNA of defined sequence," and only hypothesizes that their methods may provide dsRNA that induces interferon production. *See,* page 3, lines 3-5 of Gillespie. Moreover, not only does Gillespie fail to teach that the dsRNA they synthesize actually induces interferon production *in vivo*, this reference also clearly indicates that the toxicity of the dsRNA molecules described is not known and must be assessed. Finally, as noted above, Gillespie clearly does not contemplate *in vivo* production of the dsRNA molecules at therapeutic levels. Rather, Gillespie repeatedly teaches that biological activity (and toxicity) are to be assessed by administering already-formed dsRNA. *See, e.g.,* Section 3 of Gillespie, including page 7, lines 19-21 stating that antitumor properties can be measured by "injecting dsRNA into nude mice... ;" Section 4 on page 8 stating that "suitable test animals ... can be injected periodically with various quantities of dsRNA...;" claims 9-16, all of which are drawn to methods comprising "administering ... a therapeutically effective amount of the short dsRNAs of defined structure.... ." Clearly, Gillespie purports to provide sufficient quantities of self-complementing dsRNA by using already produced dsRNA and, moreover, does not even disclose that this strategy is actually effective.

In light of Dubensky's teaching that large quantities of antisense RNA are required to induce interferon production along with Gillespie's failure to teach that dsRNA formed *in vivo* would induce interferon production (and so should be administered after is it is already formed), the Examiner has not indicated why the skilled artisan would have had any motivation to prepare expression cassettes as claimed or why such expression cassettes would be desirable.

Furthermore, given that the references (and art as whole) teach that large quantities of the dsRNA are required to exhibit biological activity, along with unresolved questions about toxicity, the skilled artisan would not have had any reasonable expectation that sufficient quantities of dsRNA formed from self-complementation of a sequence transcribed *in vivo* would be produced to induce interferon production, and certainly would not have viewed antisense and self-complementing dsRNA as interchangeable. Therefore, the motivation to combine the references as set forth in the rejection is not present and the rejection must fail.

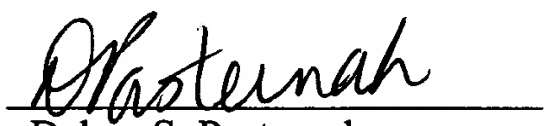
Thus, the cited references, and state of the art as a whole, does not teach or suggest the expression cassettes as claimed. Nor do the references provide the requisite motivation to combine their individual elements in the manner set forth in the claims. The alleged motivation to combine (inducing interferon production) is not present because (1) expression of multiple heterologous genes as described in Dubensky and Chada does not relate to expression of a gene and a non-gene and (2) none of the references teach or suggest *in vivo* transcription of a sequence that forms dsRNA by self-complementation *in vivo*. Without the benefit of Appellants' disclosure, a skilled artisan would have had no motivation and no reasonable expectation that substituting Gillespie's or Cella's dsRNA for Dubensky's antisense would provide sufficient amounts of dsRNA to induce interferon production when transcribed *in vivo* as claimed. Accordingly, a *prima facie* case of obviousness has not been (and indeed cannot be) presented by the Office, as such a rejection can only be based on improper hindsight reconstruction. Withdrawal of the rejection is in order.

CONCLUSION

For the reasons stated above, Appellants respectfully submit that the pending claims are non-obvious over the cited references. Accordingly, Appellants request that the rejections of the claims on appeal be reversed, and that the application be remanded to the Examiner so that the appealed claims can proceed to allowance.

Respectfully submitted,

Date: July 27, 2005

By: 
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CLAIMS APPENDIX

CLAIMS INVOLVED IN THE APPEAL

1 to 25. (canceled).

26. (previously presented): An expression cassette comprising

a promoter operably linked to a nucleic acid molecule which, when transcribed *in vivo*, forms double stranded RNA via self-complementing sequences within the RNA, wherein the double stranded RNA induces the production of interferon, and

an RNA polymerase II promoter operably linked to a nucleic acid molecule that encodes an antigen from a pathogenic agent.

27. (canceled).

28. (previously presented): The expression cassette according to claim 26 wherein said antigen is a viral antigen.

29. (original): The expression cassette according to claim 28 wherein said viral antigen is selected from the group consisting of HIV, HSV, HBV, HCV, HPV, and FIV.

30. (previously presented): The expression cassette according to claim 26 wherein said pathogenic agent is a bacteria, parasite or fungus.

31. (previously presented): The expression cassette according to claim 26 wherein said pathogenic agent is a tumor.

32. (canceled).

33. (original): The expression cassette according to claim 26 wherein said pol II promoter is selected from the group consisting of CMV, SV40, MoMLV LTR and RSV LTR.

34. (previously presented): A gene delivery vector, comprising an expression cassette according to claim 26.

35. (original): The gene delivery vector according to claim 34 where said vector is a plasmid.

36. (original): The gene delivery vector according to claim 34 where said vector is a recombinant retrovirus.

37. (original): The gene delivery vector according to claim 34 where said vector is a recombinant herpesvirus.

38. (original): The gene delivery vector according to claim 34 where said vector is a recombinant poxvirus.

39. (original): The gene delivery vector according to claim 34 where said vector is a recombinant adenovirus.

40. (original): The gene delivery vector according to claim 34 where said vector is a recombinant parvovirus.

41. (original): The gene delivery vector according to claim 34 where said vector is a recombinant alphavirus.

42. (original): The gene delivery vector according to claim 34 where said vector is a recombinant polyoma virus.

43. (previously presented): The gene delivery vector according to claim 34 where said vector is a eukaryotic layered vector initiation system vector.

44. (previously presented): A cell which contains a gene delivery vector according to claim 34.

45. (canceled).

EVIDENCE APPENDIX

No documents are submitted with this appendix.

RELATED PROCEEDINGS APPENDIX

As noted above on page 2 of this Brief on Appeal and pursuant to 37 C.F.R. § 41.37(c)(i) and (c)(x), Appellants are not aware of any related appeals or interferences which may be related to, directly affect, be directly affected by, or have any bearing on the Board's decision in the pending appeal. Accordingly, no documents are submitted with this Appendix.